#17 (13)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
KURZ, Thekla, et al.	:	Group Art Unit: 1617
Serial No.: 09/889,930	:	Examiner: Shengjun Wang
Filed: October 3, 2001	:	

For: LYOPHILISATES WITH IMPROVED RECONSTITUTIBILITY

BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on February 28, 2003, herewith are three copies of Appellants' Brief on Appeal. The attached check includes the statutory fee for the filing of this Brief and the necessary extension fee.

This is an appeal from the decision of the Examiner finally rejecting claims 13, 14, 16 and 18-28 of the above-identified application.

(1) REAL PARTY IN INTEREST

The real party in interest in the present application is Merck Patent GmbH., to whom the present application was assigned on September 28, 2001.

(2) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

(3) STATUS OF THE CLAIMS

Claims 13-30 are pending in the present application. Claims 15, 17, 29 and 30 were withdrawn from consideration. Claims 13, 14, 16 and 18-28 were rejected. Claims 13, 14, 16 and 18-28, i.e., all the rejected claims, are on appeal.

(4) STATUS OF AMENDMENTS AFTER FINAL

Amendments filed after final were not entered.

(5) SUMMARY OF THE INVENTION

The invention relates to a process for preparing a lyophilisate, having an improved dissolution rate, of three specific compounds. See specification page 1, lines 3-5 and page 4, line 22 to page 5, line 10. The process involves placing a solution of the compound to be lyophilized into a freeze drier in a vial, and then warming the solution to 30°C to 95°C followed by producing the freeze phrase from the elevated temperature. See specification page 2, lines 16-34.

(6) ISSUES

The issue presented for review in this application is the rejections under 35 U.S.C. § 103(a), i.e., whether claims 13-14, 16, and 18-20 are unpatentable over Gericke, US 5,744,641, in view of Bornstein, US 4,002,748, or Palepu, US 5,066,647, and Franks, Freeze drying of bioproducts: putting principles into practice, European Journal of Pharmaceutics and Biopharmaceutics, NL, Elsevier Science Publishers, Amsterdam, vol. 45, no. 3, 1 May 1998 (1998-05-01). pp. 221-229.

(7) GROUPING OF THE CLAIMS

For the purpose of this appeal, all claims are considered to stand or fall together.

(8) APPELLANTS' ARGUMENTS

The Office Action finally rejecting the claims, identified as paper number 11, admits that Gericke et al. does not teach the claimed process, i.e., the heating step before lyophilization.

Both Bornstein and Palepu were only cited to teach that it is desirable to make a reconstitutable lyophilisate for therapeutical purposes. These references do not provide any specific motivation toward the claimed process.

Franks, allegedly teaches that several factors, including shelf temperature, may be controlled. Allegedly the claimed process is therefore an optimization of a process for preparing a liophilisate. Applicants respectfully disagree.

None of the cited references teaches or suggests the additional step of heating the solution to be lyophilized to 30°C to 95°C just prior to freezing said solution.

Contrary to paper number 11's allegations, the additional heating step is not merely optimizing the temperature of the process or that of the shelf temperature. In a conventional freeze-drying process, the substance to be lyophilized is dissolved to form a solution by warming if necessary said substance and the solvent it is placed into to form a solution. The solution is filtered and placed into a freeze dryer and is freeze dried. The cited prior art does not teach or suggest warming the solution after the solution to be freeze dried (after optional pre-warming) and placed into the freeze dryer.

Franks teaches that the process cycle consists of four distinct stages: 1) freezing the solution, 2) primary drying, 3) secondary drying, and 4) removing the collected ice from the condenser. See Franks, page 225, second column. Nowhere does the prior art suggest or motivate an artisan to heat the solution after it is placed into the freeze dryer, but prior to the freezing step. Adding an entirely new untaught or un-suggested step into the process is more than mere optimization of the process. It would not have been obvious to one of skill in the art to even perform this step. Thus, it is not obvious to optimize said (nonexistent) step from the prior art, absent some teaching or motivation in the references to even perform said step.

Paper number 11 alleges that the step of warming the solution to a certain temperature in the freeze dryer is seen to be a matter of optimizing the starting shelf temperature of the drying process by keeping the solution in a vial at about room temperature (allegedly 30°C) for a while before lyophilization because such optimization is considered an optimization of a result effective variable. This allegation is unfounded for multiple reasons.

First, as discussed above, adding the new step of heating up the solution prior to lyophilization, but after the solution has been prepared and placed into the freeze dryer, is not merely the optimization of a result effective variable. No teaching or suggestion is present in any of the cited references for such a heating step.

Second, "room temperature" is not understood by those of skill in the art to be 30°C. Room temperature, according to Hawley's condensed Chemical Dictionary, 11th Ed., is "an ambient temperature from 20-25°C." Relevant page was submitted to the Patent Office with the Reply dated January 29, 2003.

Third, paper number 11 has not established that warming the solution to a certain temperature after the solution has been prepared, but prior to lyophilization, would be equivalent to storing the solution at the alleged room temperature of 30°C (assuming for the moment that room temperature is 30°C). And even if equivalency could be established, that would not be adequate. The law requires that prior art references provide a specific teaching, suggestion or reason to provide the necessary motivation to one of skill in the art to perform the allegedly obvious step. See *Catalina Lighting Inc. v. Lamps Plus Inc.*, 63 USPQ2d 1545 (CA FC 2002). No such specific teaching, suggestion or reason is provided in any of the references.

Paper number 11 then alleges that Franks teaches controlling shelf temperature for optimizing the results. Applicants respectfully disagree. Applicants believe, with all due respect, that the Examiner was misreading the reference. The "shelf temperature" discussed as a process parameter in Franks refers to the temperature of the "shelves" during the freezing stage (stage 1) and during the primary and secondary drying phases (stages 2 and 3). See Franks, page 225, second column, the paragraph listing of the 4 stages of the process cycle (referring to shelves in the freezing and drying stages), and especially the paragraph following said outlining of the 4 stages discussing "shelf temperatures." Franks, as discussed above, does not even consider the starting shelf temperature (i.e., product temperature prior to process cycle) as part of the process cycle for preparing a lyophilisate. See Franks, page 225, second column. Franks does not suggest at all the optimization of such product temperature prior to the process cycle as the shelf temperatures discussed refer to temperatures during the freezing and drying phases as discussed above.

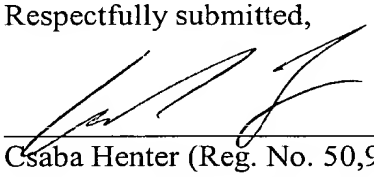
Additionally, even if Franks would have taught that the temperature of the solution can be controlled prior to the process cycle, i.e., assuming for this argument that shelf temperature refers to starting shelf temperature, nowhere does Franks specifically teach or

suggest any benefit to or relationship between such shelf temperature and final product having improved dissolution rates, i.e., amorphous properties and being reconstitutable in a particle free manner. See specification on page 2, lines 1-34. Thus, there is no teaching or suggestion to optimize such temperature as no benefit derivable therefrom is indicated.

Furthermore, the claims of the present invention are directed to specific compounds, not specifically addressed by any of the references. The prior art only generally addresses lyophilization. No teaching or motivation is present in any of the references that are specifically pertinent to the compounds of the present invention.

Reversal of the rejections is respectfully and courteously requested.

Respectfully submitted,



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APPENDIX

13. A process for preparing a lyophilisate, having an improved dissolution rate, of 2-methyl-5-methylsulfonyl-4-(1-pyrrolyl)benzoylguanidine methanesulfonate, N-[2-methyl-4,5-bis-(methylsulfonyl)benzoyl]guanidine hydrochloride or 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate, comprising dissolving 2-methyl-5-methylsulfonyl-4-(1-pyrrolyl)benzoylguanidine methanesulfonate, N-[2-methyl-4,5-bis-(methylsulfonyl)benzoyl]guanidine hydrochloride or 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate to form a solution suitable for lyophilization by optionally warming the solution to accelerate dissolution, filtering the solution, placing the solution into a freeze drier in a vial, and then warming the solution to 30°C to 95°C followed by rapidly producing the freeze phrase from the elevated temperature.

14. A process according to claim 13, wherein the solution is warmed to 30°C to 60°C.

15. A process according to claim 14, wherein the solution comprises 2-methyl-5-methylsulfonyl-4-(1-pyrrolyl)benzoylguanidine methanesulfonate.

16. A process according to claim 14, wherein the solution comprises N-[2-methyl-4,5-bis-(methylsulfonyl)benzoyl]guanidine hydrochloride.

17. A process according to claim 14, wherein the solution comprises 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate.

18. A process according to claim 14, wherein lowering the temperature to the freezing temperature takes place over from 10 minutes to 4 hours.

19. A process according to claim 14, wherein lowering the temperature to the freezing temperature takes place over from 30 minutes to 2 hours.

20. A process according to claim 14, wherein lowering the temperature to the freezing temperature takes place over from 30 minutes to 1 hour.

21. A process according to claim 14, wherein the freezing temperature is down to -70°C.

22. A process according to claim 13, wherein the freezing temperature is about -50°C.

23. A process according to claim 14 further comprising drying the solution after the lowering of the temperature.

24. A process according to claim 14, wherein the filtering is sterile filtering.

25. A process according to claim 14, wherein the temperature of the solution is at room temperature when placed into the freeze dryer.

26. A lyophilisate of 2-methyl-5-methylsulfonyl-4-(1-pyrrolyl)benzoylguanidine methanesulfonate, N-[2-methyl-4,5-bis-(methylsulfonyl)benzoyl]guanidine hydrochloride or 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate, that has been prepared by the process according to claim 13.

27 A pharmaceutical composition comprising a lyophilisate of claim 26.

28. A lyophilisate of N-[2-methyl-4,5-bis-(methylsulfonyl)benzoyl]guanidine hydrochloride, that has been prepared by the process according to claim 13.

29. A lyophilisate of 2-methyl-5-methylsulfonyl-4-(1-pyrrolyl)benzoylguanidine methanesulfonate, that has been prepared by the process according to claim 13.

30. A lyophilisate of 4-isopropyl-3-methylsulfonylbenzoylguanidine methanesulfonate, that has been prepared by the process according to claim 13.